Perioperative Vasopressor Management in Noncardiac Surgical Patients

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Arterial pressure results from the interplay between cardiac output and vascular resistance and is fundamental to ensuring tissue and organ perfusion during and after surgery. Among perfusion metrics, mean arterial pressure (MAP) serves as the principal target, as it reflects the upstream pressure driving perfusion in most organs. In the surgical patient, hypotension is common, and prolonged episodes have been consistently associated with adverse postoperative outcomes, particularly myocardial and kidney injury.[1–6]

Hypotension typically arises from reduced cardiac output or arterial tone, and its management typically includes the use of vasopressors, inotropes, and/or intravenous fluids. Vasopressors are drugs that constrict blood vessels and are usually divided into adrenergic vasopressors (ephedrine, phenylephrine, norepinephrine, and epinephrine) and nonadrenergic vasopressors (vasopressin, angiotensin II, methylene blue, and hydroxycobalamin). Vasopressors remain a cornerstone of perioperative blood pressure management used to increase and maintain vascular tone, yet optimal strategies for their use remain an area of ongoing debate. Intraoperatively, ephedrine, phenylephrine, and norepinephrine remain the most widely used vasopressors in the United States.[7,8] While ephedrine is administered exclusively as intermittent boluses, phenylephrine, norepinephrine, epinephrine, and vasopressin can all be delivered either as boluses or continuous infusions, although the latter two are less commonly administered as boluses in routine intraoperative practice. The broad range of therapeutic options at the bedside leads to considerable variability in clinical practice. Regardless of the vasopressor chosen, its impact on blood flow should be carefully assessed and excessive vasoconstriction avoided. However, practical and evidence-based guidance regarding when to initiate vasopressors, which agents to select, and how to titrate therapy remains inconsistently addressed in guidelines and is heavily influenced by individual provider experience and institutional culture. In the perioperative setting, the choice and sequencing of vasopressors remain largely guided by physiology, clinician experience, and institutional practice rather than high-level evidence. While norepinephrine, phenylephrine, and ephedrine are the most frequently used first-line agents, comparative outcome data are limited, and most randomized trials to date have been performed in septic or critically ill populations rather than surgical patients. The recently completed Vasopressors Efficacy for General Anesthesia (VEGA)-1 pilot trial suggested that norepinephrine may provide more stable blood pressure control than phenylephrine, although it was not powered to detect differences in postoperative outcomes.[9] The ongoingVEGA-2 trial (NCT06802224) will help clarify whether norepinephrine confers improved outcomes compared with phenylephrine in surgical patients. Until such evidence is available, vasopressor choice should be individualized based on the patient's hemodynamic profile (*e.g.*, preload dependency, arrhythmia risk, baseline cardiac function), surgical context, and clinician expertise, rather than a prescriptive first-, second-, or third-line hierarchy.

Furthermore, recent developments—such as peripheral norepinephrine use, individualized blood pressure targets, closed-loop vasopressor systems, and artificial intelligence–based prediction of hypotension—are beginning to reshape the landscape of vasopressor therapy.[10–13]

This review aims to synthesize current evidence and provide practical guidance for perioperative vasopressor

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Abbreviations: **MAP**, mean arterial pressure; **NO**, nitric oxide; **RCT**, randomized controlled trial; **RRT**, renal replacement therapy; **SVR**, systemic vascular resistance; **V1a/V1b/V2**, vasopressin receptor subtypes

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management in surgical patients. Our focus will be on general surgical patients managed in the operating room and intensive care unit, excluding cardiac and obstetric populations, which present distinct physiologic challenges warranting dedicated discussion.

Mechanisms of Low Vascular Resistance in Surgical Patients

In the surgical patient, low arterial tone (*i.e.*, vasodilatation) is the most common cause of hypotension.[14,15] In severe cases, vasodilatation can progress to vasodilatory shock, which is typically characterized by vasodilatation and preserved/increased cardiac output.[16] Physiologically, vascular tone is maintained by the sympathetic nervous system, the vasopressin system, and the renin–angiotensin–aldosterone system (fig. 1).[17] Hormonal ligands such as catecholamines, angiotensin II, and vasopressin bind to their respective receptors on vascular smooth muscle cells (α1, ATR1, V1a), triggering intracellular calcium release ultimately leading to the phosphorylation of myosin light chains and vascular smooth muscle cell contraction, resulting in vasoconstriction.[18] In the surgical setting, sympatholytic agents—including anesthetics used for hypnosis and neuraxial anesthesia—reduce norepinephrine stimulation and contribute to vasodilation. When vasodilation affects the arterial system, it lowers systemic vascular resistance (SVR) and reduces cardiac afterload. On the venous side, increased venous capacitance shifts stressed volume to unstressed volume, leading to a reduction in cardiac preload. Together, these effects promote hypotension.[19] In addition, tissue lesions from surgery or sepsis may also contribute to vasodilatation. In these conditions, damage-associated molecular patterns and pathogen-associated molecular patterns activate systemic inflammation,[20,21] and vasoplegia is driven by mechanisms such as nitric oxide (NO) synthesis, which inhibits smooth muscle contraction by dephosphorylating myosin. Hyperpolarization of vascular smooth muscle cells *via* potassium efflux closes calcium channels. Prolonged stimulation of adrenergic receptors is responsible for receptor desensitization that contributes to vasopressor resistance.[18,22] The three main mechanisms involved in receptor desensitization are phosphorylation, endocytosis, and downregulation.[23] Moreover, damage-associated molecular patterns released during other forms of shock (*e.g.*, hemorrhagic or cardiogenic shock) may add a vasodilatory component to the existing circulatory failure.

Vasopressors

The hemodynamic effect defining vasopressors is an increase in SVR. The primary goal of vasopressor administration is to improve organ and tissue perfusion by restoring

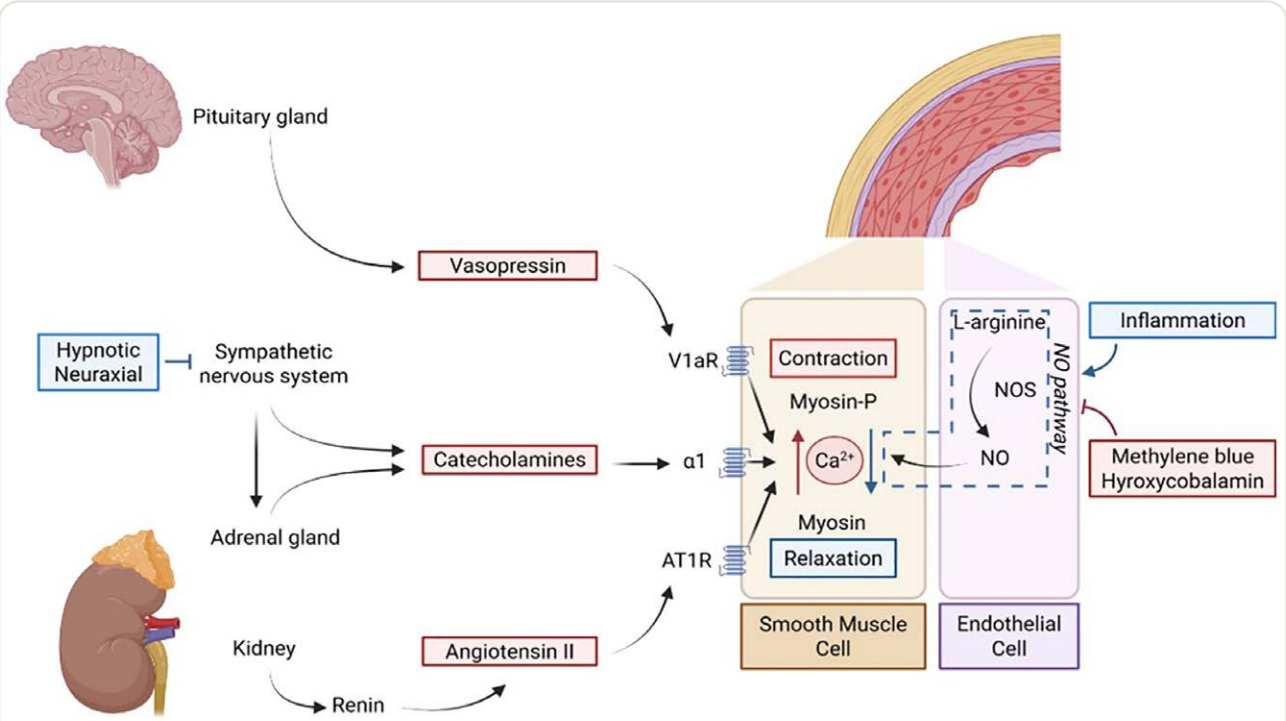

Fig. 1. Physiologic concert of the adrenergic, vasopressinergic, and renin–angiotensin systems in blood pressure homeostasis, and select mechanisms of pharmacologic vasopressors. α1, α_1-adrenergic receptor; AT1R, angiotensin type 1 receptor; β1, β_1-adrenergic receptor; β2, β_2-adrenergic receptor; V1, vasopressin 1 receptor.

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arterial tone and raising perfusion pressure, thereby reducing the risk of ischemic injury. However, the relationship between pressure and perfusion is not straightforward, as autoregulation maintains constant regional blood flow for a range of perfusion pressures in most organs.[24] Importantly, the lower limit of autoregulation—below which oxygen delivery becomes inadequate—varies between individuals and among different organs, providing, therefore, a conceptual reasoning for individualized perfusion thresholds.

The effects of vasopressors on stroke volume and cardiac output are inconsistent as they depend on loading conditions and ventriculo-arterial coupling.[25] While all vasopressors increase cardiac afterload, which may reduce cardiac output, some vasopressors can also augment cardiac output by enhancing inotropy, heart rate, or preload. As such, vasopressors may have divergent effects on perfusion, and their impact depends on the patient's overall hemodynamic profile.

Adrenergic Vasopressors

Adrenergic vasopressors are commonly used as first-line vasopressors. Their effects are dose-dependent, and their short half-life facilitates dose adaptation. Adrenergic vasopressor actions are primarily mediated through α_1 and β_1 adrenergic receptors, and the specific balance between α- and β-receptor affinities for each agent determines its clinical profile and potential side effects.

Adrenergic vasopressors increase arterial tone primarily through a stimulation of α_1 receptors. In addition, α_1 receptor activation also induces venous constriction, which may enhance cardiac preload by reducing venous capacitance, shifting unstressed volume to stressed volume, and increasing mean systemic filling pressure and venous return[26] (fig. 2). Despite higher venous resistance, increased venous return may increase stroke volume in patients in the ascending portion of the Frank–Starling curve (*i.e.*, preload-dependent). Consequently, adrenergic vasopressors are less likely to reduce cardiac output in preload-dependent patients and may increase it.[27,28] α_1 Receptors are also expressed in the pulmonary vasculature, and their activation increases pulmonary vascular resistance.[29] Stimulation of β_1-adrenergic receptors increases heart rate, inotropy, and lusitropy.[29] Thereby, β_1 stimulation supports cardiac output, and phenylephrine, which acts exclusively on α_1 receptors, carries a higher risk of reducing cardiac output due to the absence of β_1-mediated support. β_1 Activity may also enhance venous return by improving right ventricular performance. However, β_1-receptor stimulation is not without risks. It can lead to arrhythmias and increased myocardial oxygen consumption, potentially resulting in myocardial injury at high doses and especially in patients with severe coronary artery disease.[30]

Vasopressin

Vasopressin is a nondrenergic vasopressor that exerts its vasoconstrictive effects primarily through activation of V1a receptors. Unlike adrenergic vasopressors, vasopressin has no inotropic activity and minimal impact on the venous system,[26]

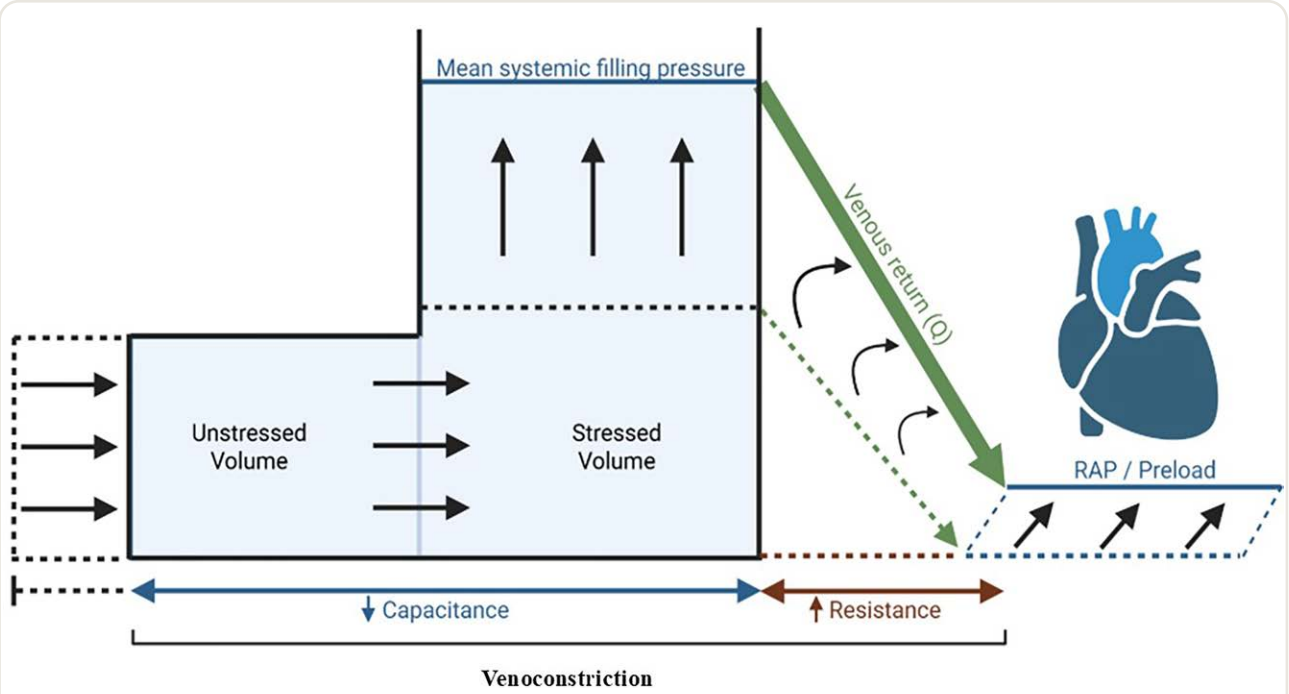

Fig. 2. Stressed *versus* unstressed blood volume: Role of venoconstriction in preload modulation. RAP, right atrial pressure.

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which may, in theory, be at risk of reducing cardiac output, particularly in preload-dependent patients. In a *post hoc* analysis (of the Vasopressin and Septic Shock Trial [VASST] trial) centered on the hemodynamic effects of vasopressin compared to norepinephrine in patients with septic shock, there was no direct decrease in cardiac index observed, but vasopressin was associated with increased use of inotropes.[31] V1a receptors are also found in the coronary and splanchnic circulations, and vasopressin has been associated with a risk of ischemic complications, particularly in the digestive tract, skin, and myocardium. However, these adverse effects are not consistently observed in clinical practice and likely depend on the dose of vasopressin and the extent to which cardiac output is maintained.[32] In cardiac surgery, there was no signal of increased ischemic complications for doses up to 0.06 U/min.[32] Vasopressin may also have theoretical endothelial and nephroprotective properties, including preferential vasoconstriction of the efferent glomerular arteriole,[33] which may help preserve glomerular filtration. Additional receptor targets include V2 receptors in the renal collecting duct, which mediate water reabsorption, and V1b receptors, which stimulate the release of adrenocorticotropic hormone. Vasopressin may also act on oxytocin and purinergic receptors, which can induce vasodilation at low-dose stimulation (this effect is reversed by V1 stimulation at higher doses).[34]

Angiotensin II

Angiotensin II is an endogenous peptide hormone that plays a key role in the renin–angiotensin–aldosterone system. Its vasopressor effects are mediated through activation of angiotensin type 1 receptors. Angiotensin II has no inotropic properties and should likely be avoided in patients with severe cardiac dysfunction. While an initial signal to higher risk of thrombotic event was suggested,[16] a meta-analysis on 1,461 patients did not find an increased incidence of thromboembolic events in patients treated with angiotensin II for shock,[35,36] although the overall quality of evidence was low. Notably, angiotensin II may offer nephroprotective effects by preferentially increasing efferent arteriolar resistance, potentially preserving glomerular filtration.[37,38] This agent has been approved in vasodilatory shock, especially septic shock and cardiopulmonary bypass vasoplegia.[39] More recently, early data suggest its safety for the management of postinduction hypotension in noncardiac surgery.[40] Patients with a relative angiotensin II deficiency and elevated renin levels appear to have better outcomes when treated with angiotensin II, although renin measurement is not widely available.[39] Finally, patients treated with angiotensin receptor blocker appear to be not responsive to angiotensin II.

Methylene Blue

Unlike traditional vasopressors, methylene blue induces vasoconstriction by inhibiting vasodilatory pathways. Specifically, methylene blue inhibits NO synthesis and soluble guanylyl cyclase enzyme, preventing the accumulation of cyclic guanosine monophosphate (GMP).[41] While some clinical efficacy has been demonstrated, the data predominantly come from small randomized controlled trials (RCTs) and observational studies and should therefore be interpreted with caution.[42] NO is a key regulator of perfusion at the endothelial level, and although increasing blood pressure, nonselective NO inhibitors increased mortality in patients with sepsis.[43,44]

Hydroxocobalamin

Hydroxocobalamin increases blood pressure through direct inhibition of NO and NO synthase, and may also antagonize hydrogen sulfide (another endogenous vasodilator). Its main reported adverse effect is acute kidney injury. Owing to their absorption spectra, both hydroxocobalamin and methylene blue can interfere with colorimetric laboratory measurements.[45,46] Currently, the literature available is mostly composed of case series and case reports, while side effects include the nonselective inhibition of the NO pathway and the risk of oxalate nephropathy.[47] Therefore, risks seem to outweigh benefits.

Impact of Vasopressor Choice on Organ Perfusion

Norepinephrine and phenylephrine are the two most commonly used vasopressors in clinical practice, and their pharmacologic effects are shown in figure 3.[7] In a historical study of 16 patients experiencing isoflurane-induced

Agent	Pharmacology	Blood Pressure	Heart Rate	SVR	Contractility	Venous Resistance	Cardiac Output
Phenylephrine	α1	↑	↓	↑	± or ↓	↑	↑ or ↓*
Norepinephrine	α1, β1 > β2	↑	± or ↑	↑	↑	↑	↑
Ephedrine	α, β (indirect & direct)	↑	↑	↑	↑	↑	↑
Epinephrine	α1, β1, β2	↑	↑	↑	↑	↑	↑
Vasopressin	V1a	↑	—	↑	—	↑	↑ or ↓
Angiotensin II	AT1R	↑	—	↑	—	↑	↑ or ↓

*depending on the preload dependence state of the patient

Fig. 3. Hemodynamic profiles of vasoactive agents.

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hypotension, a phenylephrine bolus was associated with a transient impairment of left ventricular systolic function.[48] A subsequent analysis of 269 vasopressor boluses (norepinephrine or phenylephrine) administered to 47 patients reported that norepinephrine was associated with less decreased arterial compliance and a smaller reduction in stroke volume compared to phenylephrine.[49] Contrarily, a randomized study of 60 patients by Poterman *et al.* found comparable increases in MAP and stroke volume with both agents. Although tissue perfusion (measured by near-infrared spectroscopy technology) was statistically lower in the norepinephrine group, the difference was not considered clinically relevant.[50] In the context of septic shock, a small RCT (n = 32) observed higher MAP in patients receiving norepinephrine compared to phenylephrine. However, cardiac index, systemic vascular resistance, pulmonary vascular resistance, gastric mucosal perfusion, cardiac troponin, and renal function were similar between groups.[51] A crossover study in 15 patients further highlighted differences: when switching from norepinephrine to phenylephrine, heart rate decreased, but cardiac index, SVR, and pulmonary vascular resistance remained unchanged. In addition, arterial lactate increased, creatinine clearance and indocyanine green clearance decreased. Most changes (except creatinine and gastric tonometry values) were reversed after switching back to norepinephrine. These findings suggest that phenylephrine may cause more pronounced hepatosplanchnic vasoconstriction,[52] a hypothesis supported by an additional small-scale study.[53] Finally, in a large observational study of 1,847 patients with atrial fibrillation and sepsis, phenylephrine use was associated with a very slightly lower heart rate (−4 beats/min; 95% CI, −6 to −1; $P < 0.001$), unlikely to be clinically significant.[54] In a retrospective study involving more than 8,000 patients having major noncardiac surgery, the exclusive use of intraoperative phenylephrine was associated with an increased risk of postoperative renal injury.[55] In another recent large retrospective study, the titration of phenylephrine compared to ephedrine during general anesthesia was associated with higher odds of developing postoperative delirium.[56]

In the VEGA-1 pilot RCT, which included 3,626 patients undergoing major noncardiac surgery, norepinephrine was compared to phenylephrine as a first-line vasopressor.[9] Patients in the norepinephrine group spent less time with MAP less than 65 mmHg (median [IQR]; 20 [7;43] min *vs.* 18 [6;40] min). Fluid administration was similar between groups. Importantly, the study was a feasibility trial and not powered for clinical outcomes. No significant differences in postoperative outcomes were observed.[9,57] Building upon these findings, the VEGA-2 trial (NCT06802224) is currently underway. This large RCT will enroll more than 18,000 surgical patients undergoing procedures expected to last more than 2 h. The trial will compare phenylephrine to norepinephrine as a first-line vasopressor, with acute kidney injury within 7 days as the primary outcome. While awaiting the results of VEGA-2, data are lacking to make a definitive recommendation favoring one vasopressor over the other for first-line use in surgical patients. However, several important physiologic considerations should guide clinical practice. Phenylephrine's selective α-adrenergic stimulation may be beneficial in patients with risk of arrhythmia, where β-adrenergic stimulation could be harmful. In the context of vasoplegia due to sepsis, norepinephrine is the first-line recommended vasopressor.[58] Notably, during a norepinephrine shortage in the United States, the increased use of alternative vasopressors for septic shock was associated with higher mortality.[59] Norepinephrine is also the first-line vasopressor recommended in shock of other etiologies (including vasodilatory, hemorrhagic, and cardiogenic).[60–63]

Ephedrine is commonly used as a first-line vasopressor in the operating room. Compared to phenylephrine, ephedrine has been reported to better preserve cardiac output and cerebral blood flow,[64,65] and in a retrospective cohort of 103,094 patients, ephedrine use was associated with decreased incidence of postoperative delirium compared to phenylephrine.[56] In a RCT of 120 patients aged between 60 and 90 yr undergoing knee surgery, the ephedrine group had higher cardiac output and regional cerebral oxygen saturation compared to the phenylephrine group. Additionally, postoperative delirium was reduced on day 1 in the ephedrine group, although no differences were observed on days 2 and 3 after surgery. A RCT comparing two hemodynamic management strategies for major noncardiac surgery found that a strategy using norepinephrine to target patients' baseline blood pressure as the first-line vasopressor led to less organ dysfunction than a strategy where ephedrine was used as the first-line vasopressor, with norepinephrine as the second-line agent. Blood pressure targets were, however, different between the two groups, preventing the direct comparison of vasopressors. Furthermore, the large effect with a relatively small sample size makes a type 1 error possible and a larger trial mandatory to confirm those findings.[66] The results of this large trial are expected in the coming months.[67]

To date, no large RCT has compared vasopressin to norepinephrine in the context of noncardiac surgery. In septic shock, RCTs failed to demonstrate improved renal function or survival with vasopressin use.[68–70] However, a stratified analysis of Vasopressin and Septic Shock Trial (VASSST) in patients with less severe septic shock showed lower mortality, and there was less renal replacement therapy (RRT) in the Vasopressin *vs.* Norepinephrine as Initial Therapy in Septic Shock (VANISH) study. In addition, a subsequent meta-analysis suggested a reduced need for RRT in patients treated with vasopressin.[71] In a cohort of 14,453 patients with septic shock, a reinforcement learning model suggested administering vasopressin more frequently, earlier in the course of shock, and at lower norepinephrine doses and organ failure scores.[72] In trauma patients with massive bleeding (defined as receiving 6 units or more of any

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blood product), vasopressin reduced blood product requirements,[73] suggesting a potential role in massive bleeding. As of today, experts recommend norepinephrine as the first-line vasopressor for hemorrhagic shock.[60]

Similarly, there is no strong evidence supporting improved clinical outcomes with angiotensin II in surgical patients. Its efficacy in raising blood pressure has been established in refractory vasodilatory shock through the Angiotensin II for the Treatment of High-Output Shock (ATHOS)-3 trial.[16] A *post hoc* analysis of ATHOS-3 in patients requiring RRT suggested potential nephroprotective effects, showing improved liberation from RRT and 28-day survival.[74] An improved survival with this agent was also seen in those with plasma renin concentrations greater than the population median in ATHOS3.[75] Pooled data in a meta-analysis of nonadrenergic vasopressors in perioperative vasoplegia did not show a statistically significant benefit.[76]

Practical Considerations

First-line Vasopressors

Although robust head-to-head comparative evidence is lacking, vasopressors are used in the majority of anesthetized surgical patients (50 to 90% in recent cohorts), making the choice of agent and strategy clinically highly relevant, if a meaningful difference exists between them. Most available data are extrapolated from studies in critically ill or septic patients, underscoring the urgent need for perioperative-specific research to inform evidence-based practice. Ephedrine, norepinephrine, and phenylephrine are typically used as first-line agents.

Ephedrine is administered as boluses and is suitable for peripheral administration. For repeated doses, depletion of norepinephrine stores causes tachyphylaxis, which limits the effectiveness of ephedrine after multiple administrations. Phenylephrine can be administered as iterative boluses or as a continuous infusion. Phenylephrine can be administered through peripheral venous access. Norepinephrine is most often delivered as a continuous infusion. While indicative upper-limit doses are sometimes cited, there is, *stricto sensu*, no absolute maximum dose.[77] However, reaching high doses in a surgical patient should prompt clinicians to (1) consider adding a second-line vasopressor and (2) reassess for alternative causes of hypotension such as hypovolemia, cardiogenic shock, obstructive shock, or sepsis. Peripheral administration of norepinephrine has been shown to be safe at low concentrations and doses.[1] For safety, norepinephrine—like all vasopressors—should be infused through a dedicated intravenous line, as proximally as possible to the insertion site, to minimize dead space and avoid unintentional boluses or delays in administration. Catheter size, location, and duration of infusion are also critical factors. The choice of peripheral *versus* central administration should be considered for all vasopressors, not only norepinephrine. Current expert consensus suggests that, at appropriate dilutions, norepinephrine, phenylephrine, ephedrine, vasopressin, and epinephrine may all be administered safely through a well-functioning peripheral intravenous line for short durations, particularly in urgent situations.[78–80] When feasible, transition to a central line is preferred if prolonged infusion is anticipated, higher doses are required, or multiple vasopressors must be coinfused. Concentration and dose thresholds for safe peripheral administration have been proposed in recent consensus statements, which recommend frequent site checks and use of large-bore proximal veins to mitigate risk of extravasation. In the event of extravasation, prompt management—including discontinuation of the infusion, aspiration through the catheter if possible, warm compresses, and local phentolamine infiltration—has been shown to limit tissue injury and necrosis.[81]

Last, an important but often overlooked source of variability is the distinction between norepinephrine base and its salt formulations (*e.g.*, tartrate, bitartrate, or hemitartrate).[82] Although equimolar on a pharmacologic basis, labeling practices differ internationally and even between institutions. In the United States, concentrations are typically expressed as norepinephrine base, whereas in several European countries, concentrations may reflect the salt content, resulting in numerically higher values for the same active dose. For clarity, all norepinephrine dosing in this review refers to the base formulation. Misunderstanding these differences can lead to dosing errors during bedside titration, transitions of care, or trial reporting. In clinical practice, norepinephrine is usually delivered as a continuous infusion, but it may also be given as boluses of 4 to 16 μg (using concentrations of 4 to 16 μg/ml, base equivalent).

Second-line Vasopressors and Adjuvants

Although intraoperative vasoplegia can arise from multiple etiologies, including sepsis, anaphylaxis, transfusion reactions, and drug-induced vasodilation, robust evidence is available almost exclusively for sepsis-associated vasoplegia. Accordingly, this section primarily summarizes guideline-based recommendations for the management of septic shock, followed by a brief overview of therapeutic options for other, less well-studied causes. In the context of a sepsis-induced vasodilatory shock, the Surviving Sepsis Campaign guidelines[58] suggest using vasopressin as a second-line vasopressor (instead of escalating the dose of norepinephrine) in adults with septic shock on norepinephrine with inadequate MAP levels (weak recommendation, moderate quality evidence). A threshold for initiation (from 0.25 to 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of norepinephrine-equivalent dose) is discussed in the comment as a common practice in centers from the panel, while no strong recommendation could be made on when to initiate vasopressin. Vasopressin is administered *via* continuous infusion, with a typical dose range of 0.01 to 0.03 IU/min. The guidelines also suggest using corticosteroids (weak recommendation, moderate-quality evidence).

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In cases of refractory vasodilatory shock from nonseptic etiologies, there are no established guidelines regarding the use of second-line vasopressors and adjuvants. Proposed strategies for these situations are often based on analogies with septic shock management.[61,62] Methylene blue and hydroxycobalamin are nonselective NO inhibitors. To date, neither agent has demonstrated clear benefit in surgical patients, and both may be associated with clinically significant toxicity.[47] Given the paucity of high-quality data for nonseptic causes of intraoperative vasoplegia, future research should aim to establish evidence-based protocols for perioperative contexts beyond sepsis, ideally through multicenter observational studies and pragmatic trials.

Vasopressors and/or Fluids First to Treat Hypotension?

At the bedside, the decision to administer fluids and/or vasopressors is based on multiple indirect indicators that suggest hypovolemia and/or low arterial tone (fig. 4). First, the clinical context helps determine the pretest probability of hypovolemia or low arterial tone, as certain clinical situations are more likely to be associated with these conditions (*e.g.*, active bleeding is suggestive of hypovolemia). Second, a careful analysis of the arterial waveform signal can provide additional insights. For instance, low diastolic pressure (in the absence of bradycardia) and a downward shift of the dicrotic notch suggest low arterial tone.[83] In contrast, low pulse pressure and a reduced area under the systolic curve indicate decreased stroke volume.

When cardiac output monitoring is available, the decision to administer a vasopressor is typically based on the presence of low pressure combined with preserved or elevated cardiac output. Predicting fluid responsiveness helps avoid unnecessary fluid loading, but it is crucial to verify the validity conditions of these indices before relying on them.[84] These predictors include stroke volume variations, the end-expiratory occlusion test, the tidal volume challenge, or a mini-fluid challenge.[85] Vasopressors increase cardiac output in preload-dependent patients and should not be seen as antagonistic to fluid therapy. In the intraoperative setting, vasoplegia is primarily anesthesia-induced, making vasopressor initiation often appropriate early on. However, when vasopressor doses continue to rise, this should prompt

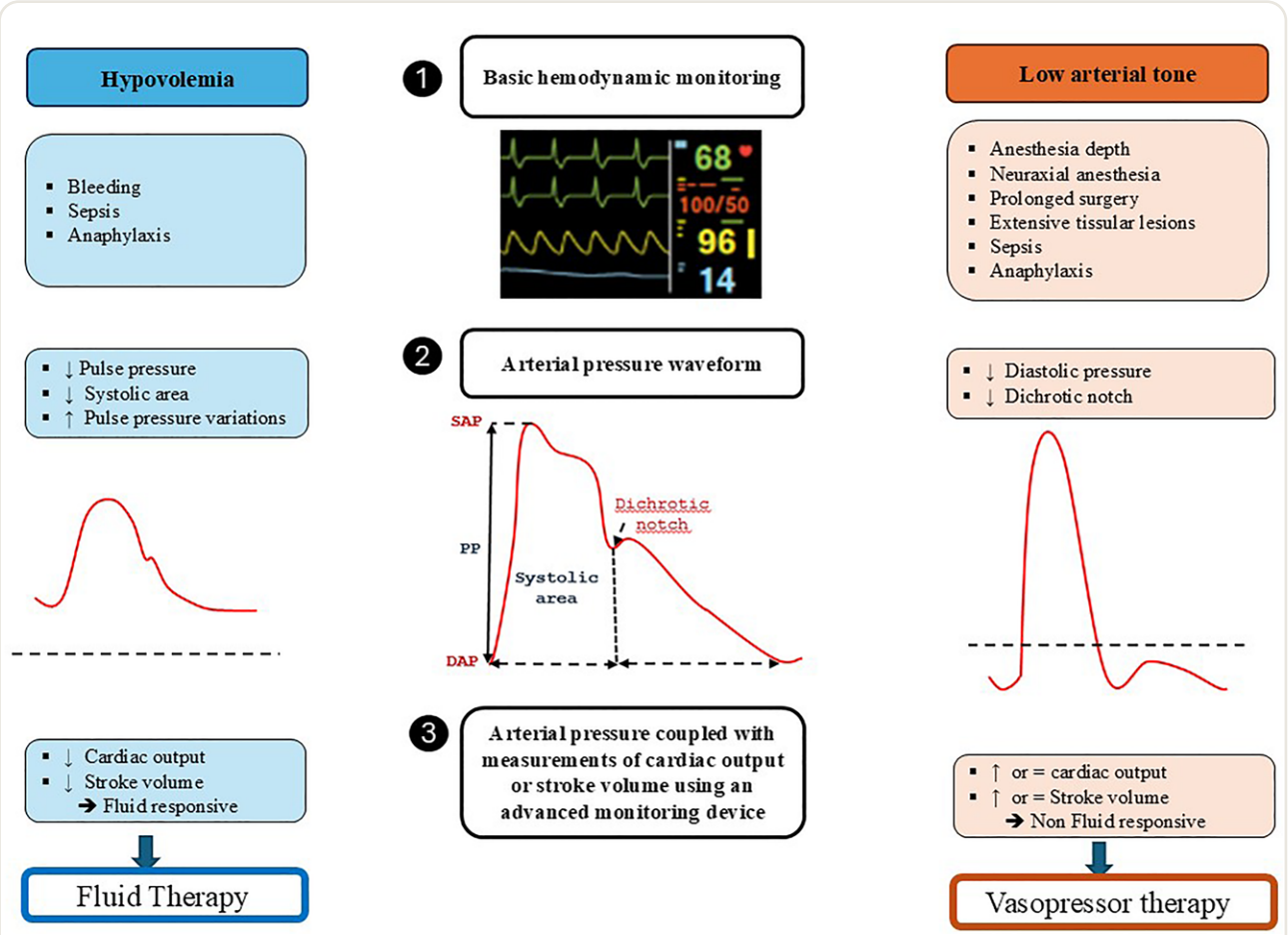

Fig. 4. Hypovolemia *versus* low arterial tone.

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reassessment of volume status and consideration of a fluid challenge to rule out unrecognized hypovolemia. Thus, vasopressors and fluids are complementary tools, guided by clinical context and dynamic response.

While invasive hemodynamic monitoring remains the accepted standard for differentiating hypovolemia from vasoplegia in high-risk patients undergoing high-risk surgery, its use is limited in most noncardiac surgical patients.[86] Consequently, many treatment decisions rely on clinical context, blood pressure trends, and indirect surrogates such as heart rate and pulse pressure.[87] Several noninvasive monitoring options may provide additional insight and could improve decision-making in this setting. Dynamic indices derived from the plethysmographic waveform (*e.g.*, pleth variability index) can help predict fluid responsiveness when conditions for validity are met.[88] Noninvasive cardiac output monitors using bioreactance, pulse contour analysis, or Doppler methods allow estimation of stroke volume and its response to fluid challenges without arterial cannulation.[89] Even simpler interventions—such as passive leg raise tests with concurrent blood pressure or plethysmographic monitoring—can guide fluid therapy and avoid unnecessary vasopressor exposure, although not unpractical in the operating room. Integration of these noninvasive tools into Enhanced Recovery After Surgery pathways may facilitate more physiologic, individualized hemodynamic management while minimizing the need for invasive lines.

Last, it is important to keep in mind that large pragmatic trials such as Cardiac Output-Guided Haemodynamic Therapy Trial (Pragmatic RCT) (OPTIMISE II) did not demonstrate significant improvements in hard outcomes with protocolized goal-directed therapy, highlighting that while such monitoring can inform decision-making, its impact on clinically meaningful outcomes and cost-effectiveness remains uncertain.[90]

Closed-loop Systems for Vasopressor Administration

Once a decision is made to initiate continuous vasopressor infusion—regardless of the initial indication—evidence clearly demonstrates that maintaining the target blood pressure is both imprecise and inaccurate in routine clinical practice. Patients are frequently exposed to periods of both under- and over-treatment, each carrying potential harm.[91] The reasons for this are intuitive. Achieving stable MAP in hypotensive surgical or critically ill patients requires frequent, fine-tuned adjustments of vasopressor dosing—often at a pace and rigor that exceeds what can be sustained by manual management. Continuous titration demands high cognitive attention and constant vigilance, competing with other essential aspects of patient care. Moreover, significant variability exists in titration practices across different providers, who often face competing clinical demands. From a systems perspective, this inter- and intrapatient variability in vasopressor titration introduces an uncontrolled source of treatment variability that is difficult to standardize.[91]

This is precisely the type of task for which automated, computer-based control is ideally suited. In this context, several studies have demonstrated the feasibility of closed-loop vasopressor systems for both surgical and critically ill patients.[92–96] Compared with manual titration, closed-loop vasopressor delivery has consistently improved time within target blood pressure ranges and reduced both hypotensive and hypertensive episodes, with benefits demonstrated in intraoperative trials, intensive care unit patients, and even preclinical animal models.[10,93–95] While these systems remain largely in prototype stages, and large randomized trials evaluating their impact on patient outcomes are still lacking, the growing interest in automated vasopressor management holds promise. Future investigations will be critical to determine whether such technologies can translate improved blood pressure control into meaningful improvements in clinical outcomes. A potential limitation of these systems is their ability to anticipate any patient-influencing factor that is external to the system's input (such as surgical incision, abdominal insufflation, clamp application, sudden bleeding, changes in patient/bed positioning).

Conclusions

While the fundamental physiology of arterial pressure regulation and the pharmacologic properties of vasopressors remain largely unchanged, the modalities of vasopressor administration continue to evolve. The safety of peripheral norepinephrine administration is now well established, expanding practical options for rapid vasopressor initiation.[97,98] Although physiologic rationale supports the use of β_1-agonist vasopressors in many clinical scenarios, outcome-based data comparing first-line agents remain limited, and consensus regarding optimal initial vasopressor choice is lacking. Similarly, further research is needed to clarify the role of second-line agents, combination regimens, and vasopressor adjuvants.

The concept of individualized vasopressor management has gained traction, with tailored blood pressure targets based on patient-specific physiology and clinical context. Hence, vasopressor therapy should be individualized and closely monitored.

At the same time, advances in artificial intelligence are transforming the field of hemodynamic prediction. Machine-learning–based systems capable of forecasting hypotensive events are now entering clinical use.[11] Currently, those devices are costly, and evidence supporting the use of these predictive systems is lacking.[99]

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Competing Interests

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